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(54) Title: BENZIMIDAZOLE VASCULAR DAMAGING AGENTS

(54) Titre: AGENTS DE DEGRADATION VASCULAIRE AUX BENZIMIDAZOLES

(57) Abstract

A group of vascular damaging agents which can be used in the preparation of medicaments for the treatment of diseases involving neovascularisation are provided. These are 5(6)-substituted benzimidazole-2-carbamates of formula (I) wherein Alk is an alkyl group, X is oxygen, sulphur, sulphinyl, sulphonyl, carbonyl (CO), thiocarbonyl (CS), sulphonyloxy, NH, iminomethylene (C=NH), N-hydroxyiminomethylene, N-alkoxyiminomethylene, dialkoxymethylene, 1,3-dioxolan-2-yl, 1,1-ethenyl, a group CHR₃, or a bond, R₁ is hydrogen, alkylaminocarbonyl or alkoxy carbonyl, R₂ is hydrogen, alkoxy carbonyl, cyanomethyl, cyanoethyl, alkoxy methyl or acetoxymethyl. R₃ is hydrogen, hydroxy, alkoxy or amino, A is an optionally substituted aromatic, optionally substituted heteroaromatic, optionally substituted heterocycloalkyl, optionally substituted alkyl or optionally substituted cycloalkyl group and the pharmaceutically acceptable salts, solvates and hydrates thereof. Most of the compounds of this group are novel, in particular those in which A is an aromatic or heteroaromatic ring with substituents, particularly substituents which are phosphates or alkylphosphates. The invention therefore provides both novel compounds and pharmacological compositions with compounds within the broad definition.

(57) Abrégé

La présente invention concerne un groupe d'agents de dégradation vasculaire convenant à la préparation de médicaments destinés au traitement d'affections impliquant une néovascularisation. Ces molécules sont des benzimidazole-2-carbamates à substitution 5(6) représentés par la formule générale (I) ou certains de leurs sels, solvates et hydrates admis en pharmacie. Dans cette formule, "alk" est un groupe alkyle. X est oxygène, soufre, sulphinyle, sulphonyle, carbonyle (CO), thiocarbonyle (CS), sulphonyloxy, NH, iminométhylène (C=NH), N-hydroxyiminométhylène, N-alkoxyiminométhylène, dialcoxy méthylène, 1,3-dioxolane-2yle, 1,1-éthényle, un groupe CHR₃ ou une liaison. R₁ est hydrogène, alkylaminocarbonyle ou alcoxycarbonyle. R₂ est hydrogène, alcoxycarbonyle, cyanométhyle, cyanoéthyle, alcoxyméthyle ou acétoxyméthyle. R₃ est hydrogène, hydroxy, alcoxy ou amino. A est un groupe éventuellement substitué, notamment aromatique, hétéroaromatique, hétérocycloalkyle, alkyle ou cycloalkyle. La plupart des composés de ce groupe entrent dans le cadre de l'invention, en particulier ceux dans lesquels A est un cycle aromatique ou hétéroaromatique à substituants, particulièrement des substituants qui sont phosphates ou alkylphosphates. L'invention concerne donc aussi bien les composés de l'invention que les compositions pharmaceutiques comportant des composés ressortissants de la définition au sens large.

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(54) Title: BENZIMIDAZOLE VASCULAR DAMAGING AGENTS			
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(57) Abstract			
<p>A group of vascular damaging agents which can be used in the preparation of medicaments for the treatment of diseases involving neovascularisation are provided. These are 5(6)-substituted benzimidazole-2-carbamates of formula (I) wherein Alk is an alkyl group, X is oxygen, sulphur, sulphinyl, sulphonyl, carbonyl (CO), thiocarbonyl (CS), sulphonyloxy, NH, iminomethylene (C=NH), N-hydroxyiminomethylene, N-alkoxyiminomethylene, dialkoxymethylene, 1,3-dioxolan-2-yl, 1,1-ethenyl, a group CHR³ or a bond, R¹ is hydrogen, alkylaminocarbonyl or alkoxy carbonyl, R² is hydrogen, alkoxy carbonyl, cyanomethyl, cyanoethyl, alkoxy methyl or acetoxymethyl. R³ is hydrogen, hydroxy, alkoxy or amino, A is an optionally substituted aromatic, optionally substituted heteroaromatic, optionally substituted heterocycloalkyl, optionally substituted alkyl or optionally substituted cycloalkyl group and the pharmaceutically acceptable salts, solvates and hydrates thereof. Most of the compounds of this group are novel, in particular those in which A is an aromatic or heteroaromatic ring with substituents, particularly substituents which are phosphates or alkylphosphates. The invention therefore provides both novel compounds and pharmacological compositions with compounds within the broad definition.</p>			

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Description

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BENZIMIDAZOLE VASCULAR DAMAGING AGENTS

This invention relates to vascular damaging agents and particularly to the use of new and known substituted benzimidazoles in the preparation of medicaments for the treatment of diseases involving neovascularisation.

Formation of new vasculature by angiogenesis is a key pathological feature of several diseases (J Folkman, New England Journal of Medicine 333, 1757-1763 (1995)). For example, for a solid tumour to grow it must develop its own blood supply upon which it depends critically for the provision of oxygen and nutrients; if this blood supply is mechanically shut off the tumour undergoes necrotic death. Neovascularisation is also a clinical feature of skin lesions in psoriasis, of the invasive pannus in the joints of rheumatoid arthritis patients and of atherosclerotic plaques. Retinal neovascularisation is pathological in macular degeneration and in diabetic retinopathy. In all these diseases reversal of neovascularisation by damaging the newly-formed vascular endothelium is expected to have a beneficial therapeutic effect.

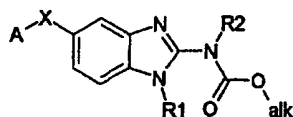
5(6)-Substituted benzimidazole-carbamates are known and have found use as antiparasitic agents (P. J. Islip in Burgers Medicinal Chemistry (M. E. Wolff ed.), Fourth Edition, Part II, p481, (1979)). Examples of such compounds include mebendazole, fenbendazole, oxbendazole, flubendazole, albendazole, cyclobendazole, parbendazole, dribendazole, luxabendazole, and etibendazole. Their mode of action for their antiparasitic action is believed to involve selective binding to tubulin of the target parasite while having little effect due to binding tubulin of the mammalian host (Biochim. Biophys. Acta 630, 271-278, (1980)). Some of these compounds have been shown to be antimitotic for cancer cells and one particular 5(6)-substituted benzimidazole-2-carbamate, nocodazole, has therefore been studied as an anticancer agent (Cancer Research, 36, 905-916 (1976)). No effects on neovasculture have been reported for any of these compounds.

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Some structurally-unrelated compounds which bind tubulin have been shown to have anti-vascular effects when given at their maximum tolerated dose (MTD) (S. A. Hill et al. Eur. J Cancer, 29A, 1320-1324 (1993)) but other tubulin-binding agents, such as docetaxel, have no vascular-damaging activity even when administered at the MTD.

The presence of tubulin-binding properties is then not predictive for antivascular activity.

According to the present invention there is provided the use of 5(6)-substituted benzimidazole-2-carbamates for the preparation of compositions for the treatment of diseases involving angiogenesis in which the 5(6)-substituted benzimidazole carbamate has the formula



I

wherein

Alk is an alkyl group

X is oxygen, sulphur, sulphinyl, sulphonyl, carbonyl (CO), thiocarbonyl (CS), sulphonyloxy, NH, iminomethylene (C=NH), N-hydroxyiminomethylene, N-alkoxyiminomethylene, dialkoxymethylene, 1,3-dioxolan-2yl, 1,1-ethenyl, a group CHR³ or a bond

R¹ is hydrogen, alkylaminocarbonyl or alkoxycarbonyl

R² is hydrogen, alkoxycarbonyl, cyanomethyl, cyanoethyl, alkoxymethyl or acetoxymethyl.

R³ is hydrogen, hydroxy, alkoxy or amino

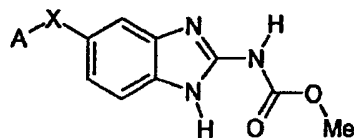
A is an optionally substituted aromatic, optionally substituted heteroaromatic, optionally substituted heterocycloalkyl, optionally substituted alkyl or optionally substituted cycloalkyl group

and the pharmaceutically acceptable salts, solvates and hydrates thereof.

Particular substituents that may be present on the group A include one or more substituents selected from a group Y, optionally substituted alkyl, (where substituents on such alkyl group may include one or more selected from hydroxy, amino, alkylamino, dialkylamino, halogen, carboxyl, SO_3H , sulphate, phosphate, alkoxycarbonyl, aralkoxycarbonyl, alkoxycarbonylamino, aminoalkylaminocarbonyl and cyano), halogen, hydroxy, amino, alkoxy, alkylthio, cyano, nitro, sulphate, isothiocyante, aryl, heteroaryl and heterocycloalkyl.

Y is a group selected from phosphate, alkylphosphate, $\text{C}(\text{O})\text{R}^4$, $\text{OC}(\text{O})\text{R}^4$, SO_2R^4 , $\text{NHC}(\text{O})\text{R}^4$, $\text{NR}^5\text{C}(\text{O})\text{R}^4$, SR^4 , $\text{S}(\text{O})\text{R}^4$, OSO_2R^4 , NHSO_2R^4 , $\text{NR}^5\text{SO}_2\text{R}^4$, SO_3H , CO_2H and CO_2R^5 where R^4 is a group selected from hydrogen, R^5 , OR^5 , NHR^5 , NR^5R^6 , aryl, heteroaryl or heterocycloalkyl such aryl, heteroaryl or heterocycloalkyl groups being optionally substituted with one or more substituents selected from alkyl, heterocycloalkyl, haloalkyl, hydroxy, nitro, cyano, amino, alkylamino, dialkylamino, halogen, carboxyl, SO_3H , sulphate and phosphate. R^5 and R^6 , which may be the same or different, are each an alkyl group optionally substituted with one or more substituents selected from hydroxy, amino, alkylamino, dialkylamino, guanidino, halogen, carboxyl, SO_3H , sulphate, phosphate, aryl and heteroaryl.

Some of the compounds usable in the invention are known, for example the following compounds within the following formula:



These compounds are

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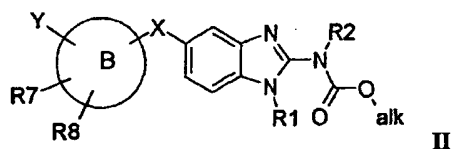
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	X	A
Fenbendazole	S	Ph
Mebendazole	CO	Ph
Albendazole	S	nPr
Oxibendazole	O	nPr
Nocodazole	CO	2-thienyl

Certain of these compounds are novel. In one embodiment the novel compounds are those of formula I in which at least one of the substituents on the group A is a group Y where Y is as hereinbefore defined. Particularly preferred are compounds defined by the formula



10 wherein

alk is an alkyl group

B is an aromatic or heteroaromatic ring

X is oxygen, sulphur, sulphinyl, sulphonyl, carbonyl (CO), thiocarbonyl (CS),

15 sulphonyloxy, NH, iminomethylene (C=NH), N-hydroxyiminomethylene, N-alkoxyiminomethylene, dialkoxymethylene, 1,3-dioxolan-2-yl, 1,1-ethenyl, a group CHR³ or a bond

R¹ is hydrogen, alkylaminocarbonyl or alkoxycarbonyl

R² is hydrogen, alkoxycarbonyl, cyanomethyl, cyanoethyl, alkoxymethyl or

20 acetoxymethyl

R³ is hydrogen, hydroxy, alkoxy or amino

Y is as hereinbefore defined

R⁷ and R⁸ are each independently H, alkyl, halogen, hydroxy, amino, alkylamino, dialkylamino, alkoxy, alkylthio, cyano, nitro, or trifluoromethyl

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with the proviso that Y is not NHC(O)Me and when B is a thiophene ring then Y is not C(O)CF_3 and when B is a 5(6)-benzimidazole ring then Y is not NHCO_2Me or NHCO_2Et

and the pharmaceutically acceptable salts, solvates, hydrates and prodrugs thereof.

As used herein the term "alkyl", alone or in combinations, means a straight or branched-chain alkyl group containing from one to seven, preferably a maximum of four, carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl and pentyl. Examples of alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy and t-butoxy. The term "halogen" means fluorine, chlorine, bromine or iodine.

The term "aryl" as used herein unless otherwise stated includes reference to a C_{6-10} aryl group which may, if desired, carry one or more substituents selected from halogeno, alkyl, haloalkyl, alkoxy, hydroxy, amino, nitro and cyano. The term "aralkoxy" means an alkoxy group substituted with an aryl group.

The term heteroaryl is defined herein as a mono- or bi-cyclic aromatic group containing one to four heteroatoms selected in any combination from N, S or O atoms and a maximum of 9 carbon atoms. Examples of heteroaryl groups include pyridyl, pyrimidyl, furyl, thienyl, pyrrolyl, pyrazolyl, indolyl, benzofuryl, benzothienyl, benzothiazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, triazolyl, quinolyl and isoquinolyl groups.

The term heterocycloalkyl includes heterocycloalkyl groups containing 3-6 carbon atoms and one or two oxygen, sulphur or nitrogen atoms. Particular examples of such groups include azetidiny, pyrrolidiny, piperidiny, homopiperidiny, piperaziny, homopiperaziny, morpholiny or thiomorpholiny groups.

The term cycloalkyl means a cycloaliphatic group containing 3-10 carbon atoms such as, for example, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

One particularly preferred group of compounds are those of formula II in which Y is a phosphate group.

- Another particularly preferred group of compounds are those of formula II in which Y is a group $\text{NR}^3\text{C}(\text{O})\text{R}^4$, R^3 is hydrogen and R^4 is a 1-aminoalkyl group which can be further substituted for example by a hydroxy group.

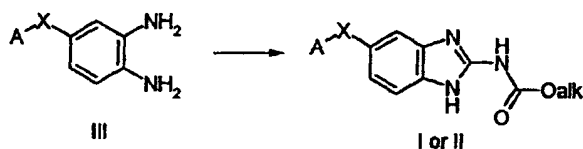
- Where one or more functional groups in compounds of formula I or II are sufficiently basic or acidic the formation of salts is possible. Suitable salts include pharmaceutically acceptable salts for example acid addition salts including hydrochlorides, hydrobromides, phosphates, sulphates, hydrogen sulphates, alkylsulphonates, arylsulphonates, acetates, benzoates, citrates, maleates, fumarates, succinates, lactates and tartrates, salts derived from inorganic bases including alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and salts derived from organic amines such as morpholine, piperidine or dimethylamine salts.

- Those skilled in the art will recognise that compounds of formulae I and II may exist as stereoisomers and/or geometrical isomers and accordingly the present invention includes all such isomers and mixtures thereof. The substituted benzimidazole group is capable of existing in tautomeric forms and the formulae I and II are intended to represent all tautomeric forms and the substituent AX- is in the 5(6) position.

- Compounds of Formula I or II may be prepared by any process known to a person skilled in the art. Compounds of Formula I or II may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols A, X and alk when used in the formulae depicted are to be understood to represent those groups described above in relation to formula I or II unless otherwise indicated. In the schemes described below it may be necessary to employ protecting groups which are then

removed during the final stages of the synthesis. The appropriate use of such protecting groups and processes for their removal will be readily apparent to those skilled in the art.

Thus according to a further aspect of the invention compounds of formulae I and II in which R^1 and R^2 are hydrogen may be prepared by treatment of a diamine of formula III with a 1,3-bis(alkoxycarbonyl)-S-alkyl isothiurea, for example 1,3-bis(methoxycarbonyl)-S-methyl isothiurea or 1,3-bis(ethoxycarbonyl)-S-methyl isothiurea, in a solvent such as an alcohol, for example methanol or ethanol, optionally mixed with water, at from about room temperature to the reflux temperature of the solvent for about 5 minutes to 6 hours. The reaction medium is preferably made acidic by the addition of for example an organic acid such as acetic acid or p-toluenesulphonic acid.



Compounds of formula III are either known or can be prepared by conventional procedures.

Compounds of formulae I and II can also be prepared from other compounds of formulae I and II by chemical modification. Example of such chemical modifications that may be applied are standard alkylation, acylation, reduction, oxidation, sulphation, aromatic halogenation, aromatic nitration, phosphorylation, hydrolysis, condensation, cleavage and coupling reactions. These reactions may be used to add new substituents, to modify existing substituents or to modify other parts of the molecule.

Thus for example a compound of formula I or II in which R^1 is hydrogen can be converted into the corresponding compounds where R^1 is alkylaminocarbonyl by

5 treatment with an alkyl isocyanate in a solvent such as tetrahydrofuran at a temperature in the range 0° to 40°C, typically room temperature.

10 In another general example a thioether group in a compound of formula I or II can be
5 converted into a sulphinyl group by treatment with periodate in an aqueous alcohol solvent such as aqueous methanol or in aqueous acetonitrile at about -20° to 50°C, for
15 about 1 to 16 h. Alternatively this conversion can be effected by treatment with one equivalent of a peracid such as 3-chloroperbenzoic acid in a chlorinated solvent such as dichloromethane or chloroform, at a temperature of about -30°C to room temperature.

20 10 In a further general example a thioether group in a compound of formula I or II can be converted into a sulphonyl group by treatment with two or more equivalents of a peracid such as 3-chloroperbenzoic acid in a chlorinated solvent such as
25 dichloromethane or chloroform, at a temperature of about -30°C to room temperature.

15 In a further general example a keto group in a compound of formula I or II can be
30 converted into a carbinol group by treatment with a reducing agent for example a hydride such as lithium aluminium hydride in an ether solvent such as diethyl ether or tetrahydrofuran at a temperature of from about 0° to the reflux temperature of the
35 20 solvent.

40 In a further general example a keto group in a compound of formula I or II can be converted into an imine by treatment with ammonia in an alcoholic solvent such as ethanol at around room temperature for an extended period, for example three weeks.

25 In a further general example a keto group in a compound of formula I or II can be
45 converted into an oxime by treatment with hydroxylamine in an alcoholic solvent such as ethanol at around room temperature to around the reflux temperature of the solvent.

50 30 In a further general example a compound of formula I or II containing a hydroxy group can be converted into the corresponding dihydrogenphosphate ester by treatment with

for example di-tert-butyl diethylphosphoramidite in the presence of a suitable catalyst for example tetrazole in a solvent such as an ether solvent for example tetrahydrofuran at a temperature in the range -40 to 40°C, conveniently at or near room temperature, followed by treatment with an oxidising agent for example 3-chloroperoxy benzoic acid or magnesium monoperoxyphthalate at a temperature in the range -78°C to 40°C preferably -65 to -10°C. The resulting intermediate phosphate triester is treated with an acid for example trifluoroacetic acid in a solvent such as a chlorinated solvent e.g. dichloromethane at a temperature in the range -30 to 40°C conveniently at or near 0°C to give the compound of formula I or II containing a dihydrogenphosphate ester.

In another general example an O-alkyl group may be cleaved to the corresponding alcohol (OH) by reaction with boron tribromide in a solvent such as a chlorinated solvent e.g. dichloromethane at a low temperature e.g. around -78°C.

In a further general example compounds of formula I or II may be alkylated by reaction with a suitable alkylating agent such as an alkyl halide, an alkyl toluenesulphonate, an alkyl methanesulphonate or an alkyl triflate. The alkylation reaction can be carried out in the presence of a base for example an inorganic base such as a carbonate e.g. caesium or potassium carbonate, a hydride such as sodium hydride or an alkoxide such as potassium t-butoxide in a suitable solvent such as an aprotic solvent e.g. dimethylformamide or an ether solvent such as tetrahydrofuran at a temperature of around -10 to 80°C.

In a further general example compounds of formula I or II containing an amine group may be acylated by treatment with a carboxylic acid and a coupling reagent, for example dicyclohexylcarbodiimide, in a suitable solvent for example an aprotic solvent such as dimethylformamide, an ether solvent such as tetrahydrofuran, a chlorinated solvent for example dichloromethane or a solvent mixture at a temperature in the range 0° to 60°, preferably about room temperature.

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In a further general example a compound of formula I or II containing an OH group can be converted into a carbamate by reaction with an alkyl isocyanate or a carbamoyl chloride in an aprotic solvent such as dimethylformamide, an ether solvent such as tetrahydrofuran, a chlorinated solvent for example dichloromethane or a solvent mixture in the presence of a base such as a tertiary amine base for example triethylamine at a temperature in the range -20° to the reflux temperature of the solvent, conveniently at or around room temperature.

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In a further general example a compound of formula I or II containing an amino group can be converted into a urea by reaction with an isocyanate or a carbamoyl chloride in an aprotic solvent such as dimethylformamide, an ether solvent such as tetrahydrofuran, a chlorinated solvent for example dichloromethane or a solvent mixture in the presence of a base such as a tertiary amine base for example triethylamine at a temperature in the range -20°C to the reflux temperature of the solvent, conveniently at or around room temperature.

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In a further general example a compound of formula I or II containing a hydroxy group can be converted into a carbonate by reaction with an chloroformate in an aprotic solvent such as dimethylformamide, an ether solvent such as tetrahydrofuran, a chlorinated solvent for example dichloromethane or a solvent mixture in the presence of a base such as a tertiary amine base for example triethylamine at a temperature in the range -20°C to the reflux temperature of the solvent, preferably at or around 0°C.

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Preparation of a compound of formula I or II as a single enantiomer or, where appropriate, diastereomer may be effected by synthesis from an enantiomerically pure starting material or intermediate or by resolution of the final product in a conventional manner.

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Acid addition salts of the compounds of formula I or II are prepared in a conventional manner by treating a solution or suspension of the free base I or II with about one

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equivalent of a pharmaceutically acceptable acid. Salts of compounds of formula I or II derived from inorganic or organic bases are prepared in a conventional manner by treating a solution or suspension of the free acid I or II with about one equivalent of a pharmaceutically acceptable organic or inorganic base. Alternatively both acid addition salts and salts derived from bases may be prepared by treatment of the parent compound with the appropriate ion-exchange resin in a standard fashion. Conventional concentration and recrystallisation techniques are employed in isolating the salts.

Compounds according to the invention are able to destroy vasculature that has been newly formed, for example tumour vasculature, while leaving unaffected normal, mature vasculature. The ability of the compounds to act in this way may be determined by the tests described hereinafter.

The compounds according to the invention are thus of particular use in the prophylaxis and treatment of cancers involving solid tumours and in the prophylaxis and treatment of diseases where inappropriate angiogenesis occurs such as diabetic retinopathy, psoriasis, rheumatoid arthritis, atherosclerosis and macular degeneration.

The compounds of the invention may be administered as a sole therapy or in combination with other treatments. For the treatment of solid tumours compounds of the invention may be administered in combination with radiotherapy or in combination with other anti-tumour substances for example those selected from mitotic inhibitors, for example vinblastine, paclitaxel and docetaxel; alkylating agents, for example cisplatin, carboplatin and cyclophosphamide; antimetabolites, for example 5-fluorouracil, cytosine arabinoside and hydroxyurea; intercalating agents for example adriamycin and bleomycin; enzymes, for example asparaginase; topoisomerase inhibitors for example etoposide, topotecan and irinotecan; thymidylate synthase inhibitors for example raltitrexed; biological response modifiers for example interferon; antibodies for example edrecolomab and antibodies against the EGFr, HER2 receptor or VEGF receptor; and anti-hormones for example tamoxifen. Such combination

treatment may involve simultaneous or sequential application of the individual components of the treatment.

For the prophylaxis and treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions selected with regard to the intended route of administration and standard pharmaceutical practice. Such pharmaceutical compositions may take a form suitable for oral, buccal, nasal, topical, rectal or parenteral administration and may be prepared in a conventional manner using conventional excipients. For example for oral administration the pharmaceutical compositions may take the form of tablets or capsules. For nasal administration or administration by inhalation the compounds may be conveniently delivered as a powder or in solution. Topical administration may be as an ointment or cream and rectal administration may be as a suppository. For parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) the composition may take the form of, for example, a sterile solution, suspension or emulsion.

The dose of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, the route of administration, the form and severity of the condition and whether the compound is to be administered alone or in combination with another drug. Thus the precise dose will be determined by the administering physician but in general daily dosages may be in the range 0.001 to 100mg/kg preferably 0.1 to 50mg/kg.

BIOLOGICAL ACTIVITY

The following test was used to demonstrate the activity and selectivity of compounds according to the invention.

Activity against tumour vasculature measured by fluorescent dye.

The following experiment demonstrates the ability of the compounds to damage tumour vasculature.

Tumour functional vascular volume in CaNT tumour-bearing mice was measured using the fluorescent dye Hoechst 33342 according to the method of Smith *et al* (Brit J Cancer 57, 247-253, 1988). The fluorescent dye was dissolved in saline at 6.25 mg/ml and injected intravenously at 10 mg/kg 6 hours or 24 hours after intraperitoneal drug treatment. One minute later, animals were killed and tumours excised and frozen; 10 μ m sections were cut at 3 different levels and observed under UV illumination using an Olympus microscope equipped with epifluorescence. Blood vessels were identified by their fluorescent outlines and vascular volume was quantified using a point scoring system based on that described by Chalkley, (J Natl Cancer Inst, 4, 47-53, 1943). All estimates were based on counting a minimum of 100 fields from sections cut at the 3 different levels. Results are expressed as percentage reduction in vascular volume compared to control.

The activity of compounds of the invention in this assay is shown in Table 1.

Table 1: Reduction in tumour vascular volume measured by fluorescent dye

Compound	Dose (mg/kg) (i.p.)	Time (h)	% Reduction in vascular volume
Fenbendazole	500	6	44
Mebendazole	500	6	56
Albendazole	500	6	51
Oxibendazole	100	6	43
Nocodazole	100	24	23
Compound of Example:			
1	500	6	81
2	500	6	80
3	50	24	22
4	50	24	53
5	50	24	99
12	50	24	51
14	50	24	39

15	50	24	61
16	50	24	56
17	50	24	62
18	50	24	47
19	50	24	88
20	50	24	69
21	50	24	74

The following non-limiting Examples illustrate the invention:

Example 1

Methyl [5(6)-(4-hydroxybenzoyl)-1H-benzimidazol-2yl]carbamate.

A solution of 3,4-diamino-4'-hydroxybenzophenone (49.6mg, 0.21mmol) and 1,3-bis(methoxycarbonyl)-S-methyl isothiurea (98mg, 0.44mmol) in ethanol (2.5ml) was treated with p-toluenesulphonic acid (7mg) and the mixture heated at reflux for 10 minutes. The mixture was cooled and the precipitate collected by filtration and washed with ethanol and hexane to give the title compound (16mg) as a white solid m.p. >258°C, ¹H-NMR (400 MHz, d6-DMSO) δ 7.80 (s, 1H), 7.65 (d, 2H, J=8Hz), 7.50 (s, 1H), 7.49 (s, 1H), 6.89 (d, 2H, J=8Hz), 3.77 (s, 3H) ppm. m/e 311 (M⁺). Anal. Calculated for C₁₆H₁₃N₃O₄: C, 61.73; H, 4.21; N 13.49. Found: C, 61.68; H, 4.18; N 13.36.

Example 2

Methyl [5(6)-(4-phosphonooxybenzoyl)-1H-benzimidazol-2yl]carbamate.

A solution of methyl [5-(4-(di-tert-butylphosphonooxy)benzoyl)-1H-benzimidazol-2yl]carbamate (1.5g, 3.0mmol) in dichloromethane (55ml) was cooled in an ice bath and treated with trifluoroacetic acid (6ml) dropwise. The mixture was allowed to warm to room temperature and stirred for 1 hour before solvents were removed under reduced pressure. The residue was triturated with ether to give the title compound (1.13g) as a white solid m.p. >258°C, ¹H-NMR (300 MHz, d6-DMSO) δ: 7.84 (s, 1H), 7.75 (d, 1H, J=9Hz), 7.57 (d, 1H, J=8Hz), 7.52 (d, J=8Hz), 7.33 (d, 1H, J=9Hz), 3.78 (s, 3H) ppm.

The methyl [5(6)-(4-(di-*tert*-butylphosphonooxy)benzoyl)-1*H*-benzimidazol-2yl]carbamate used as starting material was prepared as follows:

A solution of methyl [5(6)-(4-hydroxybenzoyl)-1*H*-benzimidazol-2yl]carbamate (100mg, 0.3mmol) in anhydrous tetrahydrofuran (1ml) stirred under a nitrogen atmosphere was treated with di-*tert*-butyl diethylphosphoramidite (74mg, 0.29mmol) and 1*H*-tetrazole (54mg, 0.78mmol) and the mixture stirred until the reaction was shown to be complete by TLC (about 1h). The cooled (-40°C) mixture was treated with 3-chloroperbenzoic acid (79mg, 0.39mmol) in dichloromethane (1ml) and stirred 10 minutes before being allowed to warm to room temperature. The mixture was washed with saturated aqueous sodium bicarbonate followed by brine and the dried (MgSO₄) organic phase concentrated under reduced pressure. The residue was chromatographed on silica gel eluting first with 4% methanol/dichloromethane then with 5% methanol/dichloromethane. Methyl [5(6)-(4-(di-*tert*-butylphosphonooxy)benzoyl)-1*H*-benzimidazol-2yl]carbamate (35mg) was obtained as a white solid m.p. 99-101°C.

Example 3

Methyl [5(6)-(4-phosphonooxyphenylthio)-1*H*-benzimidazol-2yl]carbamate

A solution of methyl [5(6)-(4-(di-*tert*-butylphosphonooxy)phenylthio)-1*H*-benzimidazol-2yl]carbamate (180mg) in anhydrous dichloromethane (10ml) at 4°C was treated with trifluoroacetic acid (1ml) and stirred for 1.5h. The mixture was allowed to warm to room temperature and concentrated under reduced pressure. Ethyl acetate was added and the mixture concentrated again. The residue was triturated with diethyl ether, washed with diethyl ether followed by acetone/water 9:1 and dried to give the title compound (134mg) as a white solid m.p. 190-193°C. Anal. Calculated for C₁₅H₁₄N₃O₆PS.3H₂O: C, 40.1; H, 4.5; N 9.3. Found: C, 40.1; H, 3.9; N 9.2.

The methyl [5(6)-(4-(di-*tert*-butylphosphonooxy)phenylthio)-1*H*-benzimidazol-2yl]carbamate used as starting material was prepared as follows:

A solution of methyl [5-(4-hydroxyphenylthio)-1*H*-benzimidazol-2yl]carbamate (200mg) in a mixture of anhydrous dimethylformamide (2ml) and anhydrous

5 tetrahydrofuran (2ml) was treated with di-*tert*-butyl diethylphosphoramidite (350mg)
and the mixture stirred for 48h at room temperature. The mixture was cooled to
10 -65°C and treated gradually with magnesium monoperoxyphthalate (850mg) so that
the temperature remained below -50°C. A saturated aqueous solution of sodium
5 bicarbonate was added, keeping the temperature below -40°C during the addition then
allowing the mixture to warm to room temperature. The mixture was extracted with
15 three portions (50ml each) of ethyl acetate and the combined extracts washed with
brine (50ml), dried (MgSO₄) and concentrated under reduced pressure. The residue
was purified by radial chromatography on silica gel eluting with
20 dichloromethane/methanol 9:1 to give methyl [5(6)-(4-(di-*tert*-
butylphosphonooxy)phenylthio)-1*H*-benzimidazol-2-yl]carbamate (180mg) as a white
foam.

Example 4

15 Methyl [5(6)-(4-aminophenylthio)-1*H*-benzimidazol-2-yl]carbamate

Methyl [5(6)-(4-(acetylamino)phenylthio)-1*H*-benzimidazol-2-yl]carbamate (602 mg,
30 1.78 mmol) was dissolved in mixture of methanol (24 ml) and hydrochloric acid (10%,
6 ml) and heated under reflux for 16h. The solution was neutralised with ammonia
solution and the methanol removed under reduced pressure. The white precipitate was
35 collected by filtration, washed with water and dried in vacuo to give 392 mg of a pale
yellow solid m.p. 282-284°C. m/e 298 (M⁺).

Example 5

40 Methyl [5(6)-(4-alanylaminophenylthio)-1*H*-benzimidazol-2-yl]carbamate

25 A suspension of methyl [5(6)-(4-(N α -*tert*-butoxycarbonylalanyl amino)phenylthio)-1*H*-
benzimidazol-2-yl]carbamate (250mg) in dichloromethane (20ml) was treated with
45 trifluoroacetic acid (4ml). The mixture was allowed to warm to room temperature and
concentrated under reduced pressure. Ethyl acetate was added and the mixture
concentrated again. The residue was triturated with diethyl ether to afford the
50 trifluoroacetic acid salt of the title compound (105mg) as a white solid m.p. 178-

182°C. m/e 485 (M⁺). Anal. Calculated for C₁₈H₁₉N₃O₃S.2C₂HF₃O₂ C; 43.1, H; 3.5, N; 11.4 Found C; 42.8, H; 3.8, N; 11.3

The methyl [5(6)-(4-(N α -*tert*-butoxycarbonylalanyl amino)phenylthio)-1*H*-benzimidazol-2-yl]carbamate used as starting material was prepared as follows:

- 5 A suspension of methyl [5(6)-(4-aminophenylthio)-1*H*-benzimidazol-2-yl]carbamate (150mg) in anhydrous tetrahydrofuran (4ml) was treated with N-*tert*-
15 butoxycarbonylalanine (100mg), cooled to -35°C and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (100mg). The mixture was allowed to warm to room temperature and stir for 16h. Water (40ml) and ethyl acetate (20ml)
20 were added and the mixture extracted with four portions of ethyl acetate (50ml each). The combined extracts were washed with brine (50ml), dried (MgSO₄) and concentrated under reduced pressure. The residue was purified on silica gel eluting with ethyl acetate to give methyl [5(6)-(4-(N α -*tert*-
25 butoxycarbonylalanyl amino)phenylthio)-1*H*-benzimidazol-2-yl]carbamate (258mg) as a white solid m.p. 222-224°C. m/e 485 (M⁺).

Example 6

Methyl [5(6)-(4-(methoxycarbonylamino)phenylthio)-1*H*-benzimidazol-2-yl]carbamate

- Methyl [5(6)-(4-aminophenylthio)-1*H*-benzimidazol-2-yl]carbamate (150 mg, 048
35 mmol) was dissolved in dimethylformamide (2 ml) and tetrahydrofuran (2 ml) and methyl chloroformate (40 mg, 0.42 mmol) added together with triethylamine (43 mg, 0.42 mmol). The solution was stirred at 20°C for 72 h and then evaporated to dryness under reduced pressure. The residue was purified by chromatography on silica gel eluting with 5 % methanol/dichloromethane to give the title compound as a white
40 solid; mp >350°C (dec.).

Example 7

Methyl [5(6)-(4-(phenylaminocarbonylamino)phenylthio)-1*H*-benzimidazol-2-yl]carbamate

- 30 Methyl [5(6)-(4-aminophenylthio)-1*H*-benzimidazol-2-yl]carbamate (150 mg, 0.48 mmol) was dissolved in dimethylformamide (2 ml) and tetrahydrofuran (2 ml) and

phenylisocyanate (56.8 mg, 0.48 mmol) added together with triethylamine (50 mg, ca. 0.5 mmol). The solution was stirred at 20°C for 12 h and the solvents removed in vacuo. The residue was purified on silica (ethyl acetate/hexane, 2:1) to give the title compound as a white solid; mp 335–340°C (dec.).m/e 433 (M⁺).

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Example 8

Methyl [5(6)-(4-(methoxycarbonyloxy)benzoyl)-1H-benzimidazol-2yl]carbamate

Methyl [5(6)-(4-hydroxybenzoyl)-1H-benzimidazol-2yl]carbamate (110 mg, 0.35 mmol) was dissolved in dimethylformamide (3.5 ml) and triethylamine (0.5 ml). The solution was cooled to 0°C and methyl chloroformate (50 mg, 0.52 mmol) added with stirring. The solution was stirred for 0.5 h at 0°C and the 1 h at 20°C and evaporated to dryness. The residue was dissolved in ethyl acetate (50 ml) and washed with sodium bicarbonate (sat., aq., 50 ml) and brine (50 ml), dried and evaporated. The residue was purified by radial chromatography on silica gel eluting with ethyl acetate/hexane, 1:1 followed by ethyl acetate to give the title compound as a white solid; mp 224–226°C (dec.).m/e 369 (M⁺).

Prepared in an analogous fashion to Example 1 were:

20 Example 9

Methyl [5(6)-(2-methoxycarbonylphenylthio)-1H-benzimidazol-2yl]carbamate from

methyl 2-(3,4-diaminophenylthio)benzoate (1.5g) and 1,3-bis(methoxycarbonyl)-S-methyl isothiurea (2.25g) there was obtained the title compound (1.51g) as a white solid m.p. 228-230 m/e 357 (M⁺). Anal. Calculated for C₁₇H₁₅N₃O₄S: C, 57.13; H, 4.23; N 11.75. Found: C, 57.39; H, 4.13; N 11.81.

45 Example 10

Methyl [5(6)-(3-methoxycarbonylphenylthio)-1H-benzimidazol-2yl]carbamate from

methyl 3-(3,4-diaminophenylthio)benzoate (246mg) and 1,3-bis(methoxycarbonyl)-S-methyl isothiurea (371mg) there was obtained the title compound (183mg) as an off-

white solid m.p. 226-228 m/e 357 (M⁺). Anal. Calculated for C₁₇H₁₅N₃O₄S: C, 57.13; H, 4.23; N 11.75. Found: C, 56.58; H, 4.31; N 11.86.

Example 11

- 5 Methyl [5(6)-(4-methoxycarbonylphenylthio)-1H-benzimidazol-2-yl]carbamate from
methyl 4-(3,4-diaminophenylthio)benzoate (830mg) and 1,3-bis(methoxycarbonyl)-S-
methyl isothiurea (1.25g) there was obtained the title compound (694mg) as an off-
white solid m.p. 280-282 m/e 357 (M⁺). Anal. Calculated for C₁₇H₁₅N₃O₄S: C, 57.13;
H, 4.23; N 11.75. Found: C, 57.21; H, 4.31; N 11.73.

Example 12

- Methyl [5(6)-(4-hydroxyphenylthio)-1H-benzimidazol-2-yl]carbamate from 4-(4-
hydroxyphenylthio)-1,2-phenylenediamine (4g) and 1,3-bis(methoxycarbonyl)-S-
methyl isothiurea (6g) there was obtained the title compound (2.4g) as a white solid
m.p. 202-204°C. m/e 315 (M⁺). ¹H-NMR (400 MHz, d₆-DMSO) δ 3.74 (s, 3H_s), 6.76
and 7.2 (AA'BB', 4H, J = 8.6 Hz), 7.03 (dd, 1H, J = 1.7, 6.6 Hz), 7.29 (d, 1H, J =
1.4 Hz), 7.34 (d, 1H, J = 8.3 Hz), 9.68 (b, 1H_s), 11.67 (b, 2H) ppm.

Example 13

- 20 Methyl [5(6)-(4-(acetylamino)phenoxy)-1H-benzimidazol-2-yl]carbamate from 4-(4-
(acetylamino)phenoxy)-1,2-phenylenediamine (1.02g) and 1,3-bis(methoxycarbonyl)-
S-methyl isothiurea (2.67g) there was obtained the title compound (0.93g) as a white
solid m.p. 304-306°C m/e 340 (M⁺). Anal. Calculated for C₁₇H₁₆N₄O₄: C, 60.00; H,
4.74; N 16.46. Found: C, 60.03; H, 4.72; N 16.42.

Prepared in an analogous fashion to Example 3 was:

Example 14

- Methyl [5(6)-(4-phosphonooxyphenoxy)-1H-benzimidazol-2-yl]carbamate from methyl
[5(6)-(4-(di-*tert*-butylphosphonooxy)phenoxy)-1H-benzimidazol-2-yl]carbamate

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(200mg) there was obtained the title compound (140mg) as a white solid m.p. 272-275°C.

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Example 15

5 Methyl [5(6)-(4-hydroxy- α -hydroxyiminobenzyl)-1H-benzimidazol-2yl]carbamate
15 [5(6)-(4-hydroxybenzoyl)-1H-benzimidazol-2yl]carbamate (100 mg, 0.32 mmol) was added to a solution of hydroxylamine (0.8 mmol) in MeOH (20 mL, prepared by treatment of hydroxylamine hydrochloride (0.64 g, 1.6 mmol) and NaOH (0.14g, 1.6 mmol) followed by filtration). The solution was heated at 70°C for 36 h, cooled and
20 water (30 ml) added. The solution was filtered and washed with ether and the solid triturated with methanol to yield the title compound (40 mg) as a white solid; mp 288-290°C.

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The following known compounds were prepared by literature methods:

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Example 16: Methyl [5(6)-(4-(acetylamino)phenoxy)-1H-benzimidazol-2yl]carbamate

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Example 17: Methyl [5(6)-(4-aminophenoxy)-1H-benzimidazol-2yl]carbamate

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20 Example 18: Methyl [5(6)-(3-aminophenoxy)-1H-benzimidazol-2yl]carbamate

Example 19: [5(6)-(4-hydroxybenzoyl)-1H-benzimidazol-2yl]carbamate

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Example 20: [5(6)-(2-hydroxybenzoyl)-1H-benzimidazol-2yl]carbamate

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Example 21: [5(6)-(3-hydroxybenzoyl)-1H-benzimidazol-2yl]carbamate

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Claims

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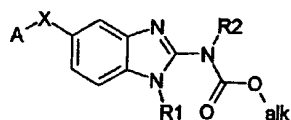
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CLAIMS

1. Use of vascular damaging agents in the preparation of compositions for the treatment of diseases involving angiogenesis, characterised in that the agents are 5(6)-substituted benzimidazole-2-carbamates of formula:



wherein

- Alk is an alkyl group
- X is oxygen, sulphur, sulphinyl, sulphonyl, carbonyl (CO), thiocarbonyl (CS), sulphonyloxy, NH, iminomethylene (C=NH), N-hydroxyiminomethylene, N-alkoxyiminomethylene, dialkoxymethylene, 1,3-dioxolan-2-yl, 1,1-ethenyl, a group CHR³ or a bond
- R¹ is hydrogen, alkylaminocarbonyl or alkoxycarbonyl
- R² is hydrogen, alkoxycarbonyl, cyanomethyl, cyanoethyl, alkoxymethyl or acetoxymethyl.
- R³ is hydrogen, hydroxy, alkoxy or amino
- A is an optionally substituted aromatic, optionally substituted heteroaromatic, optionally substituted heterocycloalkyl, optionally substituted alkyl or optionally substituted cycloalkyl group

and the pharmaceutically acceptable salts, solvates and hydrates thereof.

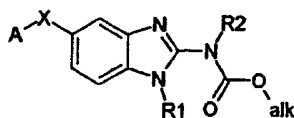
2. A use according to claim 1 wherein the substituent on A is selected from (a) alkyl substituted by one or more of hydroxy, amino, alkylamino, dialkylamino, halogen, carboxyl, SO₃H, sulphate, phosphate, alkoxycarbonyl, aralkoxycarbonyl, alkoxycarbonylamino, aminoalkylaminocarbonyl and cyano; or halogen, hydroxy,

amino, alkoxy, alkylthio, cyano, nitro, sulphate, isothiocyanate, aryl, heteroaryl or heterocycloalkyl; or (b) a group Y selected from

phosphate, alkylphosphate, $C(O)R^4$, $OC(O)R^4$, SO_2R^4 , $NHC(O)R^4$,
 $NR^4C(O)R^4$, SR^4 , $S(O)R^4$, OSO_2R^4 , $NHSO_2R^4$,

- 5 $NR^5SO_2R^4$, SO_3H , CO_2H and CO_2R^5 where R^4 is selected from hydrogen, R^5 , OR^5 ,
 15 NHR^5 , NR^5R^6 , aryl, heteroaryl or heterocycloalkyl such aryl, heteroaryl or
 heterocycloalkyl groups being optionally substituted with one or more substituents
 selected from alkyl, heterocycloalkyl, haloalkyl, hydroxy, nitro, cyano, amino,
 20 alkylamino, dialkylamino, halogen, carboxyl, SO_3H , sulphate and phosphate wherein
 10 R^5 and R^6 , which may be the same or different, are each an alkyl group optionally
 substituted with one or more substituents selected from hydroxy, amino, alkylamino,
 dialkylamino, guanidino, halogen, carboxyl, SO_3H , sulphate, phosphate, aryl and
 25 heteroaryl.

- 15 3. A 5(6)-substituted benzimidazole-2-carbamate of formula



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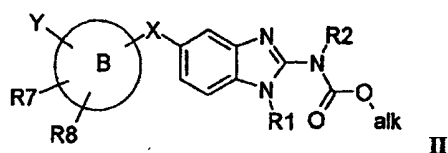
wherein

- 20 Alk is an alkyl group
 X is oxygen, sulphur, sulphinyl, sulphonyl, carbonyl (CO), thiocarbonyl (CS),
 40 sulphonyloxy, NH, iminomethylene (C=NH), N-hydroxyiminomethylene, N-
 alkoxyiminomethylene, dialkoxymethylene, 1,3-dioxolan-2-yl, 1,1-ethenyl, a group
 25 CHR^3 or a bond
 45 R^1 is hydrogen, alkylaminocarbonyl or alkoxycarbonyl
 R^2 is hydrogen, alkoxycarbonyl, cyanomethyl, cyanoethyl, alkoxymethyl or
 acetoxymethyl.
 50 R^3 is hydrogen, hydroxy, alkoxy or amino

A is an optionally substituted aromatic, optionally substituted heteroaromatic,
optionally substituted heterocycloalkyl, optionally substituted alkyl or optionally
substituted cycloalkyl group

in which at least one substituent is Y selected from phosphate, alkylphosphate,
C(O)R⁴, OC(O)R⁴, SO₂R⁴, NHC(O)R⁴, NR⁵C(O)R⁴, SR⁴, S(O)R⁴, OSO₂R⁴,
NHOSO₂R⁴, NR⁵SO₂R⁴, SO₃H, CO₂H and CO₂R⁵ where R⁴ is selected from hydrogen,
R⁵, OR⁵, NHR⁵, NR⁵R⁶, aryl, heteroaryl or heterocycloalkyl such aryl, heteroaryl or
heterocycloalkyl groups being optionally substituted with one or more substituents
selected from alkyl, heterocycloalkyl, haloalkyl, hydroxy, nitro, cyano, amino,
alkylamino, dialkylamino, halogen, carboxyl, SO₃H, sulphate and phosphate wherein
R⁵ and R⁶, which may be the same or different, are each an alkyl group optionally
substituted with one or more substituents selected from hydroxy, amino, alkylamino,
dialkylamino, guanidino, halogen, carboxyl, SO₃H, sulphate, phosphate, aryl and
heteroaryl and the pharmaceutically acceptable salts, solvates and hydrates thereof.

4. A carbamate according to claim 3 of formula:



wherein

alk is an alkyl group

B is an aromatic or heteroaromatic ring

X is oxygen, sulphur, sulphinyl, sulphonyl, carbonyl (CO), thiocarbonyl (CS),

sulphonyloxy, NH, iminomethylene (C=NH), N-hydroxyiminomethylene, N-
alkoxyiminomethylene, dialkoxymethylene, 1,3-dioxolan-2-yl, 1,1-ethenyl, a group
CHR³ or a bond

R¹ is hydrogen, alkylaminocarbonyl or alkoxycarbonyl

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R^2 is hydrogen, alkoxy carbonyl, cyanomethyl, cyanoethyl, alkoxy methyl or
acetoxymethyl

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R^3 is hydrogen, hydroxy, alkoxy or amino

Y is as hereinbefore defined

- 5 R^7 and R^8 are each independently H, alkyl, halogen, hydroxy, amino, alkylamino,
15 dialkylamino, alkoxy, alkylthio, cyano, nitro, or trifluoromethyl

20

with the proviso that Y is not NHC(O)Me and when B is a thiophene ring then Y is
not C(O)CF_3 and when B is a 5(6)-benzimidazole ring then Y is not NHCO_2Me or
10 NHCO_2Et

25

and the pharmaceutically acceptable salts, solvates, hydrates and prodrugs thereof.

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5. A carbamate according to claim 4 in which Y is a phosphate group.

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6. A carbamate according to claim 4 in which Y is NHC(O)R^4 wherein R^4
is a 1-aminoalkyl group.

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7. A composition for treatment of diseases involving angiogenesis
20 comprising at least one 5(6)-substituted benzimidazole-2-carbamate of formula I as
defined in claim 1 in an amount sufficient to damage new vasculature.

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8. A composition according to claim 7, wherein the carbamate is as
defined in claim 2.

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9. A composition according to claim 7, wherein the carbamate has a
formula II as defined in claim 3.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/GB00/00099 (22) International Filing Date: 14 January 2000 (14.01.2000) (30) Priority Data: 9900752.8 15 January 1999 (15.01.1999) GB (60) Parent Application or Grant ANGIOGENE PHARMACEUTICALS LTD. [/]; (). DAVIS, Peter, David [/]; (). DAVIS, Peter, David [/]; (). BAILLIE, Iain, C. ; ().		Published
(54) Title: BENZIMIDAZOLE VASCULAR DAMAGING AGENTS (54) Titre: AGENTS DE DEGRADATION VASCULAIRE AUX BENZIMIDAZOLES (57) Abstract <p>5(6)-substituted benzimidazole-2-carbamates of formula (I) wherein Alk is an alkyl group, X is oxygen, sulphur, sulphinyl, sulphonyl, carbonyl (CO), thiocarbonyl (CS), sulphonyloxy, NH, iminomethylene (C=NH), N-hydroxyiminomethylene, N-alkoxyiminomethylene, dialkoxymethylene, 1,3-dioxolan-2yl, 1,1-ethenyl, a group CHR₃ or a bond, R₁ is hydrogen, alkylaminocarbonyl or alkoxy carbonyl, R₂ is hydrogen, alkoxy carbonyl, cyanomethyl, cyanoethyl, alkoxy methyl or acetoxymethyl. R₃ is hydrogen, hydroxy, alkoxy or amino, A is an optionally substituted aromatic, optionally substituted heteroaromatic, optionally substituted heterocycloalkyl, optionally substituted alkyl or optionally substituted cycloalkyl group and the pharmaceutically acceptable salt, solvates and hydrates thereof, can be used in the preparation of medicaments for the treatment of diseases involving neovascularisation.</p> (57) Abrégé <p>La présente invention concerne un groupe d'agents de dégradation vasculaire convenant à la préparation de médicaments destinés au traitement d'affections impliquant une néovascularisation. Ces molécules sont des benzimidazole-2-carbamates à substitution 5(6) représentés par la formule générale (I) ou certains de leurs sels, solvates et hydrates admis en pharmacie. Dans cette formule, "alk" est un groupe alkyle. X est oxygène, soufre, sulphinyle, sulphonyle, carbonyle (CO), thiocarbonyle (CS), sulphonyloxy, NH, iminométhylène (C=NH), N-hydroxyiminométhylène, N-alcoxyiminométhylène, dialcoxyméthylène, 1,3-dioxolane-2yle, 1,1-éthényle, un groupe CHR₃ ou une liaison. R₁ est hydrogène, alkylaminocarbonyle ou alcoxycarbonyle. R₂ est hydrogène, alcoxycarbonyle, cyanométhyle, cyanoéthyle, alcoxyméthyle ou acétoxyméthyle. R₃ est hydrogène, hydroxy, alcoxy ou amino. A est un groupe éventuellement substitué, notamment aromatique, hétéroaromatique, hétérocycloalkyle, alkyle ou cycloalkyle. La plupart des composés de ce groupe entrent dans le cadre de l'invention, en particulier ceux dans lesquels A est un cycle aromatique ou hétéroaromatique à substituants, particulièrement des substituants qui sont phosphates ou alkylphosphates. L'invention concerne donc aussi bien les composés de l'invention que les compositions pharmaceutiques comportant des composés ressortissants de la définition au sens large.</p>		

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(71) Applicant (for all designated States except US): ANGIOGENE PHARMACEUTICALS LTD. [GB/GB]; 14 Plowden Park, Aston Rowant, Watlington, Oxfordshire OX9 5SW (GB).			
(72) Inventor; and (75) Inventor/Applicant (for US only): DAVIS, Peter, David [GB/GB]; 10 Aston Park, Aston Rowant, Watlington OX9 5SW (GB).		Published With international search report.	
(74) Agents: BAILLIE, Iain, C. et al.; Langner Parry, 52-54 High Holborn, London WC1V 6RR (GB).		(88) Date of publication of the international search report: 16 November 2000 (16.11.00)	
(54) Title: BENZIMIDAZOLE VASCULAR DAMAGING AGENTS			
<p style="text-align: right;">(I)</p>			
(57) Abstract			
<p>5(6)-substituted benzimidazole-2-carbamates of formula (I) wherein Alk is an alkyl group, X is oxygen, sulphur, sulphonyl, sulphonyl, carbonyl (CO), thiocarbonyl (CS), sulphonyloxy, NH, iminomethylene (C=NH), N-hydroxyiminomethylene, N-alkoxyiminomethylene, dialkoxymethylene, 1,3-dioxolan-2-yl, 1,1-ethenyl, a group CHR³ or a bond, R¹ is hydrogen, alkylaminocarbonyl or alkoxy carbonyl, R² is hydrogen, alkoxy carbonyl, cyanomethyl, cyanoethyl, alkoxy methyl or acetoxymethyl. R³ is hydrogen, hydroxy, alkoxy or amino, A is an optionally substituted aromatic, optionally substituted heteroaromatic, optionally substituted heterocycloalkyl, optionally substituted alkyl or optionally substituted cycloalkyl group and the pharmaceutically acceptable salt, solvates and hydrates thereof, can be used in the preparation of medicaments for the treatment of diseases involving neovascularisation.</p>			

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/00099

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/4184 A61P9/00 C07D235/32 C07F9/6506				
According to International Patent Classification (IPC) or to both national classification and IPC				
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K A61P C07D C07F				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched				
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
X	KRUSE L I ET AL: "Synthesis, tubulin binding, antineoplastic evaluation, and structure-activity relationship of oncodazole analogues" JOURNAL OF MEDICINAL CHEMISTRY, vol. 32, no. 2, February 1989 (1989-02), pages 409-17, XP002142971 the whole document, also page 412, table I, compound 28 — —/—	1-9		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.				
<input checked="" type="checkbox"/> Patent family members are listed in annex.				
* Special categories of cited documents: <table border="0"> <tr> <td> "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed </td> <td> "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "Z" document member of the same patent family </td> </tr> </table>			"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "Z" document member of the same patent family
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Date of the actual completion of the international search 21 July 2000		Date of mailing of the international search report 07/08/2000		
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Aillard, M		

INTERNATIONAL SEARCH REPORT

Inter- national Application No

PCT/GB 00/00099

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LACEY E ET AL: "Activity of benzimidazole carbamates against L1210 mouse leukaemia cells: Correlation with in vitro tubulin polymerization assay" BIOCHEMICAL PHARMACOLOGY, vol. 34, no. 19, 1985, pages 3603-3605, XP002056333 ISSN: 0006-2952 the whole document	1,2,7,8
X	CHEMICAL ABSTRACTS, vol. 84, no. 21, 24 May 1976 (1976-05-24) Columbus, Ohio, US; abstract no. 144640r, DE BRABANDER M J ET AL: "The effects of methyl '5-(2-thienylcarbonyl)-1H- benzimidazol-2-yl!carbamate, (R 17934; NSC 238159), a new synthetic antitumoral drug interfering with microtubules, on mammalian cells cultured in vitro" page 26; XP002143095 cited in the application abstract & CANCER RES., vol. 36, no. 3, 1976, pages 905-16,	1,2,7,8
X	US 3 965 113 A (BEARD C C ET AL) 22 June 1976 (1976-06-22) the whole document	3,4,7-9
X	US 3 694 455 A (DUNN G L) 26 September 1972 (1972-09-26) the whole document	3,7-9
X	DE 23 48 104 A (FARBWERKE HOECHST AG) 3 April 1975 (1975-04-03) the whole document, particularly compounds VIII	3
X	DE 21 64 690 A (FARBWERKE HOECHST AG) 12 July 1973 (1973-07-12) the whole document, particularly example 19	3,4,7-9
X	DE 23 32 343 A (FARBWERKE HOECHST AG) 16 January 1975 (1975-01-16) the whole document, particularly example 20	3,4,7-9
	-/-	

INTERNATIONAL SEARCH REPORT

Inter- national Application No
PCT/GB 00/00099

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KHAN A M ET AL: "Studies on enteric anthelmintics: Impact of single point structural change on the activity profile" ZEITSCHRIFT FÜR NATURFORSCHUNG, B, vol. 43, no. 2, February 1988 (1988-02), pages 233-7, XP002142972 the whole document	3,4,7-9
X	RAEYMAEKERS A H M ET AL: "Synthesis and anthelmintic activity of alkyl-(5-acyl-1H-benzimidazol-2-yl) carbamates" ARZNEIMITTEL-FORSCHUNG, vol. 28(I), no. 4, 1978, pages 586-94, XP002142973 the whole document, particularly page 591, table 5, 22nd entry	3,4,7-9
X	ABUZAR S ET AL: "Synthesis and anthelmintic activity of 2,2'-disubstituted 5,5'-dibenzimidazolylsulfides and sulfones" ARZNEIMITTEL-FORSCHUNG, vol. 36(I), no. 3, March 1986 (1986-03), pages 416-9, XP002142974 the whole document	3,7-9
X	DATABASE CROSSFIRE 'Online! Beilstein Institut zur Foerderung der Chemischen Wissenschaften; XP002142975 Beilstein Registry Number 4595458 & INDIAN J. CHEM. SECT. B, vol. 19, no. 7, 1980, pages 536-8,	3,4
X	DATABASE CROSSFIRE 'Online! Beilstein Institut zur Foerderung der Chemischen Wissenschaften; XP002142976 Beilstein Registry Number 5651135 & INDIAN J. CHEM. SECT. B, vol. 24, 1985, pages 754-60,	3,4,7-9
X	DATABASE CROSSFIRE 'Online! Beilstein Institut zur Foerderung der Chemischen Wissenschaften; XP002142977 Beilstein Registry Number 5622648 & INDIAN J. CHEM. SECT. B, vol. 24, 1985, pages 747-53,	3,4,7-9
	-/-	

INTERNATIONAL SEARCH REPORT

Internat'l Application No

PCT/GB 00/00099

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE 'Online! Beilstein Institut zur Foerderung der Chemischen Wissenschaften; XP002142978 Beilstein Registry Number 5669479, 5670801, 5667941, 5667940, 5665325 & INDIAN J. CHEM. SECT. B, vol. 24, 1985, pages 730-2,	3,7-9
X	DATABASE CROSSFIRE 'Online! Beilstein Institut zur Foerderung der Chemischen Wissenschaften; XP002142979 Beilstein Registry Number 4615289, 4609187 & INDIAN J. CHEM. SECT. B, vol. 23, no. 12, 1984, pages 1274-8,	3,7-9
X	DATABASE CROSSFIRE 'Online! Beilstein Institut zur Foerderung der Chemischen Wissenschaften; XP002142980 Beilstein Registry Number 6009722, 6007941, 6007769 & INDIAN J. CHEM. SECT. B, vol. 24, 1985, pages 178-81,	3,7-9
A	US 5 763 473 A (ELOKDAH H M ET AL) 9 June 1998 (1998-06-09) the whole document	1

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-4, 7-9 (all partly)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty of claims 1-4 and 7-9. So many documents were retrieved that it is impossible to determine which parts of these claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search and an exhaustive search report over the whole breadth of said claims are impossible. Consequently, the documents cited in the search report with regard to said claims should only be considered as forming a representative sample of the revealed documents.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/00099

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3965113 A	22-06-1976	AR 214701 A	31-07-1979
		AT 332422 B	27-09-1976
		AT 1075073 A	15-01-1976
		AU 6367573 A	19-06-1975
		CA 1023750 A	03-01-1978
		CH 592634 A	31-10-1977
		DE 2363348 A	18-07-1974
		DK 151628 B	21-12-1987
		ES 421928 A	16-10-1976
		FR 2212149 A	26-07-1974
		GB 1434830 A	05-05-1976
		IE 40141 B	28-03-1979
		IL 43859 A	31-12-1976
		IN 138651 A	06-03-1976
		IN 138645 A	06-03-1976
		JP 49094671 A	09-09-1974
		NL 7317798 A	02-07-1974
		AR 216037 A	30-11-1979
		AR 221816 A	31-03-1981
		AT 341822 B	27-02-1978
		AT 835875 A	15-06-1977
		AT 332883 B	25-10-1976
		AT 1075173 A	15-02-1976
		AU 6367473 A	19-06-1975
		BE 809234 A	28-06-1974
		BE 809235 A	28-06-1974
		CA 1032171 A	30-05-1978
		CH 608006 A	15-12-1978
		CH 613955 A	31-10-1979
		CS 187390 B	31-01-1979
		CS 187395 B	31-01-1979
		DD 112450 A	12-04-1975
		DE 2363351 A	11-07-1974
		DE 2366069 A	10-11-1977
		DE 2366070 C	11-06-1987
		DK 137329 B	20-02-1978
		ES 421927 A	01-01-1977
		ES 445257 A	01-10-1977
		FR 2212150 A	26-07-1974
		FR 2272665 A	26-12-1975
		GB 1456497 A	24-11-1976
		GB 1455728 A	17-11-1976
		HK 8280 A	14-03-1980
		HU 169272 B	28-10-1976
		IE 40046 B	28-02-1979
		IL 43860 A	31-05-1977
		IN 138650 A	06-03-1976
US 3694455 A	26-09-1972	NONE	
DE 2348104 A	03-04-1975	AU 7358674 A	25-03-1976
		BE 820324 A	25-03-1975
		DD 115493 A	05-10-1975
		DK 502574 A	02-06-1975
		FI 276974 A	26-03-1975
		FR 2244504 A	18-04-1975
		JP 50058072 A	20-05-1975
		NL 7412464 A	27-03-1975

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/00099

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 2348104	A	NO 743436 A SE 7412041 A US 3928375 A	21-04-1975 26-03-1975 23-12-1975
DE 2164690	A	12-07-1973	
		AT 320638 B AU 465226 B AU 5048672 A BE 793358 A BG 22080 A BG 20591 A CA 1017750 A CH 583710 A CH 580080 A CS 173650 B CS 173615 B DD 109219 A DD 110760 A DK 130293 B EG 11122 A ES 409860 A FI 54299 B FR 2166048 A GB 1360180 A HU 165060 B IE 37855 B IL 41170 A IT 1043888 B JP 50033067 B JP 48080558 A KE 2613 A KR 7800116 A MX 3541 E MY 9276 A NL 7217532 A, B NO 137092 B PH 10285 A RO 71503 A SE 395890 B SU 492086 A SU 493967 A US 3954791 A US 3984561 A YU 177773 A ZA 7209076 A	25-02-1975 18-09-1975 27-06-1974 27-06-1973 25-11-1976 05-12-1975 20-09-1977 14-01-1977 30-09-1976 28-02-1977 28-02-1977 20-10-1974 12-01-1975 03-02-1975 31-05-1977 16-11-1975 31-07-1978 10-08-1973 17-07-1974 28-06-1974 26-10-1977 31-01-1977 29-02-1980 27-10-1975 29-10-1973 15-04-1976 15-04-1978 10-02-1981 31-12-1976 29-06-1973 19-09-1977 05-11-1976 30-01-1981 29-08-1977 15-11-1975 28-11-1975 04-05-1976 05-10-1976 13-11-1981 28-11-1973
DE 2332343	A	16-01-1975	
		AT 342041 B AT 525274 A CA 1031781 A CH 614706 A DK 341474 A ES 427455 A HU 168527 B IT 1056735 B JP 1163768 C JP 50040564 A JP 57058343 B NL 7408394 A SE 7408321 A	10-03-1978 15-07-1977 23-05-1978 14-12-1979 17-03-1975 16-07-1976 28-05-1976 20-02-1982 26-08-1983 14-04-1975 09-12-1982 30-12-1974 27-12-1974

Form PCT/ISA/210 (patent family annex) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/00099

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 2332343 A		YU 178074 A	18-06-1982
US 5763473 A	09-06-1998	NONE	